REMARKS

The Official Action mailed March 31, 2005, has been carefully studied. The applicants having presented a new set of claims above, the claims in the application are now 4, 8, 9, 11 and 14-25. These claims define novel and unobvious subject matter under §§102 and 103, and therefore should be allowed. Applicants again respectfully request favorable reconsideration and allowance.

New claims 14-25 have been added, with 14-24 being directed to the product, and claim 25 being directed to a method of making. These claims are patentable for the same reasons as the other claims, as will be pointed out below.

Claims 1-13 have been rejected under the first paragraph of §112. The rejection is respectfully traversed.

First, applicants question why claim 4 was included in this rejection in view of the fact that claim 4 does not contain the criticized terminology, contrary to what is stated in the Official Action. Applicants assume that the inclusion of claim 4 in this rejection was an inadvertent error.

As regards the other claims, except for claims 8 and 9 which have now been amended to depend from claim 4, applicants need not at present further address this rejection in view of the deletion of such other claims. For the record,

however, applicants respectfully note that such deletion is made without prejudice of any kind, applicants reserving their rights to reinsert such claims and/or similar claims in future prosecution, e.g. in a continuing application, if applicants choose to do so. Accordingly, such deletion is made without dedication, disclaimer, abandonment, waiver, forfeiture, renunciation, concession or surrender of any kind.

Claims 1, 2, 4-8 and 10-12 have also been rejected under the first paragraph of §112 as lacking enablement. The rejection states that while the specification is "enabling for reduction of clotting in a patient, it does not reasonably provide enablement for preventing clotting". This rejection is respectfully traversed.

The objective of the claimed invention is to prevent/reduce blood clotting in association with transplantation of islets of Langerhans. The term "clotting preventing" is used as a synonym to "clotting reducing" (reducing the likelihood of blood clotting). Clotting prevention is a multi-factorial process comprising reduced activation of the complement cascade and increased capacity of antitrombin absorption on the cell surface leading to a reduced generation of trombin-antithrombin (TAT) complex. Therefore it is not possible, or even necessary, to minimize the clotting to zero, i.e. to totally prevent clotting. The

objective of the present invention is to reduce/inhibit the effect of clotting to an extent that the cells maintain their ability to produce/secrete insulin.

The point is that the terminology "preventing clotting" is perfectly correct because the agents in question **do prevent some significant amount of clotting**, and are known to do so. The terminology does not imply that **all** clotting is prevented. Nevertheless, in deference to the examiner's views and to avoid needless argumentation, the terms "prevent" and "preventing" have been changed to "inhibit" and "inhibiting". No change in substance is intended by this amendment, i.e. the meaning of the claims remains the same.

Withdrawal of the rejection is in order and is respectfully requested.

Claims 1-9, 12 and 13 have been rejected under the second paragraph of §112. This rejection is respectfully traversed.

Applicants do not understand this rejection. Is the examiner saying that "isolating islets" does not provide antecedent basis for "isolated islets"? If so, applicants would invite the examiner's attention to MPEP 2173.05(e), with reference to *Ex parte Porter*, 25 USPQ2d 1144, 1145 (BPAI 1992) which makes clear that antecedent basis need only be understandable, not perfect. Nevertheless, on the assumption

that the criticism does indeed stem from the examiner's contention that "isolating islets" does not provide adequate antecedent basis for "isolated islets", claim 4 has been amended above to change the word "isolating" to "isolated". Again, no change in substance is intended by such amendment.

Insofar as the criticism of claim 9 is concerned, certainly "clotting preventing agent" provides full and adequate support for "preventing agent" as recited in claim 9. There can be no other possible meaning. Again, the examiner's attention is respectfully invited to MPEP 2173.05(e). Nevertheless, and again to avoid needless argumentation, claim 9 has been amended to eliminate any possibility of confusion, even though any confusion would be extremely remote.

Withdrawal of the rejection is in order and is respectfully requeted.

Claims 1-4, 10 and 11 have been rejected as anticipated by Wagner. The rejection is respectfully traversed for the reasons of record which are respectfully repeated by reference.

The claimed invention does not eliminate the need for immunosuppressive therapy. In the description on page 1, lines 13-15, and page 2, lines 11-14, it is understood that the present invention is not evaluating the effect of heparin coated cells on the immunology system and graft rejection.

The present invention deals with the prevention of blood clotting in order to preserve the biological function (insulin secretion) of the isolated islets. Further, in the Declaration submitted on March 2, 2004, at page 4, last section, the inventors state that the invention relies on well-established protocols for immunosuppression. Therefore, the examiner's comments concerning transplant rejection is of no relevance in the present application.

Wagner describes microcapsules used in transplantation surgery. The microcapsules are made of organic material (polylysin complexed alginate) and allow release of active substances, in particular insulin and insulin related substances. These capsules are filled with islets of Langerhans, and the objective is to have a controlled release of insulin through the microcapsules. The disclosed microcapsules are approximately 0.5 mm in diameter, and have an inner volume which is many times larger than the volume of the encapsulated islets (see page 6, line 10 and page 7, lines 6-8, of the English translation).

It should be noted that Wagner discloses no other alternative than encapsulation (see for example page 5, line 7-10 and page 6, line 7-9, of the English translation). In particular, it should be noted that despite the fact that there is a discussion of the degree of free space inside the

capsules and the effect thereof on e.g. the diffusion behaviour, the only alternative suggested for enhancing the efficiency is to make the capsule smaller (see page 7, lines 9-13, of the English translation). Nowhere in Wagner is it even remotely suggested that the islets be coated in the sense of the present invention.

The presently claimed invention comprises surface modified insulin producing islets. These islets are coated, prior to transplantation, with a clotting preventing agent. The coating procedure is an irreversible modification of the islets where heparin molecules, or other clotting preventing agents, are adsorbed to the cell surface in the form of a permeable coating incapable of preventing immunological cross-reactions. Thus, it is submitted that the teachings of Wagner leads the skilled person away from the present invention.

Support for the new claims 14 and 15 are found in the specification at page 3, lines 12-18 in conjunction with page 9, Example 3. Thereby, the claimed invention is clearly distinguished from the subject matter of Wagner.

The Office Action contains a paragraph at the middle of page 12 which is entitled to "Response to Declaration under 37 CFR 1.132", but appears to be directed to an allegation by the PTO that applicants' specification does not support certain claim terminology, in particular that the cells in

applicants' claims are not artificially encapsulated. First, as noted above, claim 4 contains no such language. Also, claim 11, lumped together with claims 1-10 also contains no such language.

In effect, the PTO has brushed aside the Declaration filed March 2, 2004, in spite of the fact that the Declarants are experts in the art who are entitled to present expert opinion which must be considered, and further in spite of the fact that the Declarants submitted statements of **fact** based on their knowledge. Thus, the Declarants state on page 2 of their Declaration executed in February of 2004 as follows:

> We state as fact that coating according to our invention is absolutely not the same as encapsulating according to Wagner and Soon-Shiong. Coating in accordance with our invention of the present U.S. Patent application does not result in encapsulation, but instead results in a linkage between the islets and the heparin or other clotting preventing agent, i.e. the "coating" according to our invention results in the isolated islets being modified by irreversible adsorption with the heparin, a physical condition which is entirely unlike encapsulation with a polymeric material as disclosed by Wagner and Soon-Shiong.

The Declarants have thus stated as fact that the claimed subject matter is inherently different from the applied prior art. By what right does the PTO ignore such a statement of fact? Respectfully, there is no justification for the PTO position.

Applicants respectfully note that what is inherently present in a disclosure is there, even though such inherent material is not explicitly stated.

The Declarants have stated as fact that, unlike the cited and applied prior art, no encapsulation occurs in the present invention. Their Declaration states as follows at the middle of page 5:

> In the case where the islets have been modified by e.g. the Corline Heparin surface (e.g. our Example 3), there are no prerequisites that would lead anyone skilled in the art to conclude that such a procedure involving simple mixing would represent encapsulation. The procedure implies (and results in) attachment to the biological structure of the islets of individual high-molecular weight molecules, with no semi-permeable function.

This is furthermore explained in the following paragraph spanning pages 5 and 6 of the Declaration as follows:

> The U.S. Examiner has questioned what is meant by "artificial" encapsulation, and how our invention differs. We have in part addressed this above, and now add that what is "artificial" in Wagner and Soon-Shiong is the creation of an artificial shell of polymeric material, i.e. the capsule which encapsulates whatever component is intended to be encapsulated. In our invention, contrary to Wagner and Soon-Shiong, no such capsule is formed. The heparin in our invention does not encapsulate the islets. Even when a heparin-conjugate with alginate, e.g. the Corline heparin conjugate of Example 3 of our above-identified U.S. Patent application, is used, encapsulation of the islets does not occur.

These statements of fact cannot be properly brushed aside or ignored or disregarded.

Applicants respectfully note that a Declaration under 37 CFR 1.132 is **evidence**, and evidence is not to be ignored.

See *In re Khelghatian*, 150 UPSQ 661,663, footnote 2 (CCPA 1966), wherein Judge Rich, speaking for the Court, and commenting on the Supreme Court's decisions in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459, and *United States v. Adams*, 383 U.S. 39, 148 USPQ 479, stated as follows: "In our view the Court there said nothing at all about 'doubtful cases,' nor in any way suggested that any record evidence should not be accorded its full probative weight…. Such an approach [brushing off a Declaration because the examiner "is satisfied" that the invention is unpatentable] is reminiscent of the proverbial "don't bother me with the facts, my mind is made up" method of decision and has, we think, no place in the application of 35 U.S.C. 103. We therefore remain of the view that the law requires consideration of all ***evidence***, properly submitted, …." (emphasis in original; bracketed material added). Thus, all evidence is to be considered.

Also see *In re Alton*, 37 USPQ2d 1578, 1583 (Fed Cir 1996), relating to declarations of fact. Also see *Ex parte*

Copping, 180 USPQ 475, 476, relating to opinion affidavits from experts.

Applicants respectfully repeat that the **evidence** in this case is that the cited and applied prior art, including Wagner, neither anticipate nor make obvious the claimed invention, and there is neither evidence nor good reasoning to the contrary.

Applicants request that the rejection under §102 based on Wagner be withdrawn, as Wagner simply does not anticipate applicants' invention.

Claims 1 and 5-7 have been rejected under §102 as being anticipated by Lenschow. This rejection is respectfully traversed for the reasons of record, respectfully repeated by reference.

Claims 4, 8 and 9 have not been rejected on the basis of Lenschow, so this rejection need not be addressed at the present time. As noted above, the rejected claims have been deleted without prejudice to applicants' rights to pursue these claims at a later date if applicants choose to do so.

To the extent that this reference might be deemed to apply to any of applicants' new claims, applicants note that the Lenschow et al publication describes a method for protection from graft rejection (see abstract). The authors administered CTLA4Ig to mice rather than treating the islets

in vitro, i.e. the CTLA4Ig was administered systemically to the mice and not added to the islets to be transplanted. Lenschow et al do not mention blood clotting or prevention thereof. Thus, this publication would not lead the skilled person to the presently claimed invention.

Lenschow was also addressed in the aforementioned Declaration in the paragraph spanning pages 7 and 8 thereof, where the Declarants stated as follows:

> The third citation relied upon by the U.S. examiner is a publication in the name of Lenschow et al. This publication is in certain respects even more remote from our invention than are Wagner and Soon-Shiong, because the authors simply administered CTLA4Ig to mice rather than treating the islets, i.e. the CTLA4Ig was administered systemically to the mice and not to the islets. The Lenschow et al publication therefore has nothing to do with our invention.

As indicated above, a Declaration is **evidence**. The PTO has presented no contrary evidence, nor any good reasoning which would contradict the aforementioned Declaration evidence.

The rejection at the top of page 10 states (or seems to state) that the rejected claims are inherently anticipated by Lenschow. This makes no sense at all to applicants. As stated above and previously, Lenschow simply administered the active agent to mice rather than treating the islets, and that has nothing to with the present invention. Insofar as inherency is concerned, reliance by the PTO on inherency in a

reference requires that such inherency must be reasonably certain. For example, please see *In re Brink*, 164 USPQ 247, 249:

> Absent a showing [by the PTO] of some **reasonable certainty** of inherency, the rejection... under 35 U.S.C. 102 must fail. (emphasis added)

Also see *Ex parte Cyba*, 155 USPQ 756, 757 (1967), and *In re Oelrich*, 212 USPQ 323, 326 (1981). There is no reasonable certainty that anything done by Lenschow et al and disclosed in the Lenscow publication would provide anything identical or even similar to the present invention. Therefore, inherency in Lenschow is neither inevitable nor reasonably certain, and no inherency exists which can be relied upon.

Withdrawal of the rejection is in order and is respectfully requested.

Claims 1-4, 10 and 11 have been rejected again as anticipated under §102 by Soon-Shiong. This rejection is respectfully traversed for the reasons of record.

It is well known that the main reason for using encapsulation is to avoid immunological reactions aiming at eliminating the need for immunosuppressive therapy. In Soon-Shiong, an encapsulation system is disclosed (see col. 3, lines 53-61, and abstract) which comprises compounds which are capable of undergoing free redical polymerization e.g. by

using certain sources of light. The objective of Soon-Shiong is to provide an encapsulation which allows delivery of substances from the insides of the capsule, i.e. drug delivery or insulin secretion from encapsulated islets of Langerhans, while providing immunoprotection. The Soon-Shiong patent does not disclose features of clotting prevention, and thus teaches away from the presently claimed invention.

Applicants respectfully add, as already noted above, that the PTO is unjustified in ignoring the evidence of the Declaration of record where the Declarants stated as fact as follows at page 7:

> We therefore state as fact that our islets, after "coating" with heparin, are not encapsulated.
>
> Our heparin-modified islets can be obtained by simple mixing of heparin or heparin complex with the islets, as in Example 3 of our U.S. patent application. On the other hand, in Wagner and Soon-Shiong there are required operations, which are the main focus of these documents, for the creation of the capsule shells, e.g. extrusion in a two-phase coaxial flow system according to Example 20 of Soon-Shiong, or an emulsification technique with a photo polymerization as set forth in Example 19 of Soon-Shiong.

The examiner is not justified in speculating contrary to the statements of fact in the Declaration of record.

Withdrawal of the rejection based on Soon-Shiong under §102 is in order and is respectfully requested.

As the examiner has correctly pointed out, undersigned made an error at the bottom of page 7 of the "Second Preliminary Amendment for Continued Examination" filed on March 2, 2004. There had been a rejection imposed under §103, and undersigned apologizes for the error.

The Office Action of March 31, 2005, states at the middle of page 11 that the rejection under §103 based on Soon-Shiong is maintained and repeated.

Paper No. 5 was the Office Action mailed February 26, 2003. The only rejection under §103 in such Office Action was the rejection of claim 5 as obvious under §103 from Soon-Shiong. As understood, the PTO position in this regard is that the substitution of an inhibitor platelet activation in place of the clot preventing agent of Soon-Shiong would have been obvious. The rejection is respectfully traversed.

Nevertheless, claim 5 has now been deleted without prejudice as indicated, but new claim 18 specifies an inhibitor of platelet activation. However, claim 18 is patentable at least for the same reasons as claim 14 from which it depends.

The prior art documents made of record and not relied upon have been noted, along with the implication that such documents are deemed by the PTO to be insufficiently

pertinent to warrant their application against any of applicant's claims.

Favorable reconsideration and allowance are earnestly solicited.

Respectfully submitted,

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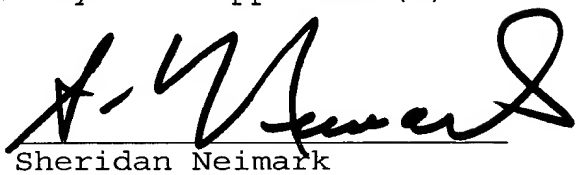
By 
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